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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/938,597 | 08/27/2001 | Frederick A. Gage | 106996 | 2731 |

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| EXAMINER | |
|---|---|
| DAVIS, RUTH A | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1651 | |

DATE MAILED: 11/19/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/938,597 | GAGE ET AL. | |
| | Examiner | Art Unit | |
| | Ruth A. Davis | 1651 | |

*-- Th MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *26 August 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-43* is/are pending in the application.

4a) Of the above claim(s) *21-43* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. §§ 119 and 120**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a)☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *1101* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

## DETAILED ACTION

### *Election/Restrictions*

Applicant's election with traverse of Group I, claims 1 -- 20, filed August 23, 2003 is acknowledged. The traversal is on the ground(s) that the method of group II is a species of group I and would therefore necessarily be searched with the invention of group I. Applicant further argues that there is no serious burden to examine all of the groups together. This is not found persuasive because as indicated by the separate classification, the groups have acquired a separate status in the art as a separate subject for inventive effect and require independent searches. While the search for one group may overlap that of another group, an overlapping search is not a coextensive search. Further, a reference that would anticipate the invention of one group would not necessarily anticipate or even make obvious another group.

The requirement is still deemed proper and is therefore made FINAL.

Claims 21 – 43 are withdrawn from consideration as being drawn to non-elected subject matter.

### *Claim Rejections - 35 USC § 112*

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 4 – 5 and 9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 4 is drawn to a method for treating an organ, however is rendered vague and indefinite because the phrases "until it appears that thrombolysis is substantially complete"; "measured parameters"; and "acceptable limits" have not been adequately defined by the claim language or specification. Moreover, it is unclear how applicant intends to limit the scope of the invention by these phrases.

Claim 5 is rendered vague and indefinite for reciting "other recombinant tissue plasminogen activators" and "other mutant tPAs" because the phrases are not adequately defined by the claim language or specification. It is unclear what applicant intends to include or exclude from these phrases as no examples or definitions have been set forth.

Claim 9 is rendered vague and indefinite for reciting "or from about 10 to about 30 or more Units" because it is unclear what the phrase is meant to encompass. For example, 10 – 30 units more than what? Could "or more" be any number of units more than 10 – 30, or more than 58,000,000?

***Claim Rejections - 35 USC § 102***

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 1, 4 – 6, 9 and 20 are rejected under 35 U.S.C. 102(a) as being anticipated by Yamauchi et al. (2000).

Applicant claims a method for treating an organ with a thrombolytic agent to promote thrombolysis, the method comprising perfusing the organ with a perfusion solution comprising a thrombolytic agent. Perfusion is conducted until thrombolysis is substantially complete and parameters are within acceptable limits. The thrombolytic agent is selected from streptokinase, urokinase, alteplase, tenecteplase, tissues plasminogen activators, anistreptase, anisoylated streptokinase, reteplase, and mutant tissue plasminogen activators; specifically streptokinase at 5000 – 58,000,000 IU or about 10 – 30 more units. The organ is selected from a heart, liver, kidney, lung, pancreas and intestine

Yamauchi teaches methods wherein livers are flushed (perfused) with solutions containing streptokinase, wherein microvascular procurement of the liver is improved (abstract, methods) and thrombus formation is prevented (p.1781, Results).

The reference anticipates the claimed subject matter.

5. Claims 1, 4 – 5, 9, 11 and 20 are rejected under 35 U.S.C. 102(a) as being anticipated by Luh et al. (2000).

Applicant claims a method for treating an organ with a thrombolytic agent to promote thrombolysis, the method comprising perfusing the organ with a perfusion solution comprising a thrombolytic agent. Perfusion is conducted until thrombolysis is substantially complete and

parameters are within acceptable limits. The thrombolytic agent is selected from streptokinase, urokinase, alteplase, tenecteplase, tissues plasminogen activators, anistreptase, anisoylated streptokinase, reteplase, and mutant tissue plasminogen activators; and is administered at 5000 – 58,000,000 IU or about 10 – 30 more units. The perfusion solution further comprises a vasodilator and the organ is selected from a heart, liver, kidney, lung, pancreas and intestine.

Luh teaches methods wherein lungs are perfused with a solution containing heparin, urokinase (thrombolytic agents), PGE1, and NO (vasodilators) wherein thrombus formation was inhibited (abstract). Specifically, lungs are perfused with a solution containing 15,000 IU heparin and 120,000 IU urokinase (p.2020).

The reference anticipates the claimed subject matter.

6. Claims 1, 4 – 6 and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Dubrul et al. (US 5380273).

Applicant claims a method for treating an organ with a thrombolytic agent to promote thrombolysis, the method comprising perfusing the organ with a perfusion solution comprising a thrombolytic agent. Perfusion is conducted until thrombolysis is substantially complete and parameters are within acceptable limits. The thrombolytic agent is selected from streptokinase, urokinase, alteplase, tenecteplase, tissues plasminogen activators, anistreptase, anisoylated streptokinase, reteplase, and mutant tissue plasminogen activators; specifically streptokinase. The organ is selected from a heart, liver, kidney, lung, pancreas and intestine.

Dubrul teaches methods for dissolving thrombi within intestines, wherein a thrombolytic agent such as urokinase is dispensed (abstract). Other thrombolytic agents are named to include streptokinase and tissue plaminogen activators (col.1 line 48-57).

The reference anticipates the claimed subject matter.

7. Claims 1, 4 – 10 and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Gundry et al. (1992).

Applicant claims a method for treating an organ with a thrombolytic agent to promote thrombolysis, the method comprising perfusing the organ with a perfusion solution comprising a thrombolytic agent. Perfusion is conducted until thrombolysis is substantially complete and parameters are within acceptable limits. The thrombolytic agent is selected from streptokinase, urokinase, alteplase, tenecteplase, tissues plasminogen activators, anistreptase, anisoylated streptokinase, reteplase, and mutant tissue plasminogen activators; specifically streptokinase at 10,000 – 1,500,000 IU, 100,000 – 300,000 IU, 5000 – 58,000,000 IU or about 10 – 30 more units, or 250,000 IU. The organ is selected from a heart, liver, kidney, lung, pancreas and intestine.

Gundry teaches a method wherein a heart is harvested and perfused with 200,000 units of streptokinase, wherein clots are dissolved (or effects thrombolysis) (abstract).

The reference anticipates the claimed subject matter.

8. Claims 1, 4 – 10 and 17 – 20 are rejected under 35 U.S.C. 102(b) as being anticiapted by Pineo et al. (1987).

Applicant claims a method for treating an organ with a thrombolytic agent to promote thrombolysis, the method comprising perfusing the organ with a perfusion solution comprising a thrombolytic agent. Perfusion is conducted until thrombolysis is substantially complete and parameters are within acceptable limits. The thrombolytic agent is selected from streptokinase, urokinase, alteplase, tenecteplase, tissues plasminogen activators, anistreptase, anisoylated streptokinase, reteplase, and mutant tissue plasminogen activators; specifically streptokinase at 10,000 – 1,500,000 IU, 100,000 – 300,000 IU, 5000 – 58,000,000 IU or about 10 – 30 more units, or 250,000 IU. The organ is perfused for 1 – 20 hours, at least 4 hours, 4 – 12 hours and is selected from a heart, liver, kidney, lung, pancreas and intestine.

Pineo teaches a method wherein a kidney is infused with streptokinase to effect thrombolysis (abstract). Specifically, 100,000 – 520,000 IU were administered over 16.5 hours (p.1223).

The reference anticipates the claimed subject matter.

9. Claims 1, 3 – 4, 12 and 15 – 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Yland (1996).

Applicant claims a method for treating an organ with a thrombolytic agent to promote thrombolysis, the method comprising perfusing the organ with a perfusion solution comprising a thrombolytic agent. The perfusion comprises connecting the organ to a perfusion circuit and recirculating the solution through the organ and is conducted until thrombolysis is substantially complete and parameters are within acceptable limits. The perfusion circuit has a systolic pressure of less than 60 mm Hg, and is recirculated at about 2 – 10C or about 5C for 1 – 20

hours, at least 4 hours, or 4 -- 12 hours. The organ is selected from a heart, liver, kidney, lung, pancreas and intestine.

Yland teaches machine perfusion is effective for organ and kidney preservation (abstract). Specifically, that machine perfusion can be high or low flow at 6 – 9C. Yland teaches methods wherein kidneys are removed, high and low flow machine flushed (perfused) with heparin (a thrombolytic agent) at 0 – 4C for about 72 hours (p.536, Materials and Methods). Perfusion pressure are 30 – 40 mm Hg with a controlled perfusion curcuit (p.536, Equipment).

The reference anticipates the claimed subject matter.

***Claim Rejections - 35 USC § 103***

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 1 - 5 and 9 – 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Luh in view of Fahy (US 5472876).

Applicant claims a method for treating an organ with a thrombolytic agent to promote thrombolysis, the method comprising perfusing the organ with a perfusion solution comprising a thrombolytic agent. The organ is removed from a human; or is selected from a heart, liver, kidney, lung, pancreas and intestine. The thrombolytic agent is selected from streptokinase, urokinase, alteplase, tenecteplase, tissues plasminogen activators, anistreptase, anisoylated streptokinase, reteplase, and mutant tissue plasminogen activators; and is administered at 5000 – 58,000,000 IU or about 10 – 30 more units, or 250,000 IU. Perfusion comprises connecting the organ to a perfusion circuit and recirculating the solution through the organ and is conducted until thrombolysis is substantially complete and parameters are within acceptable limits; the perfusion circuit has a systolic pressure of less than 60 mm Hg, 45 – 60 mm Hg or about 50 mm Hg and the perfusion solution is recirculated at about 2 – 10C or about 5C for 1 – 20 hours, at least 4 hours or 4 – 12 hours. The perfusion solution further comprises a vasodilator.

Luh teaches methods wherein lungs are perfused with a solution containing heparin, urokinase (thrombolytic agents), PGE1, and NO (vasodilators) wherein thrombus formation was inhibited (abstract). Specifically, lungs are perfused with a solution containing 15,000 IU heparin and 120,000 IU urokinase (p.2020). Luh further teaches that urokinase and PGE1 are added to perfusion solutions to improve organ vasodilation and thrombolysis (p.2025).

Luh does not teach the method wherein the lungs are perfused with a circuit. However, Fahy teaches methods for machine perfusing organs wherein the organ is flushed (or perfused) with a perfusion solution comprising heparin (thrombolytic agent) and vasodilators (col.23 line 4-9). The excised organs are perfused at pressures of 20 – 70 mmHg (col.24 line 32-38) at 0 – 15C (col.24 line 58-62) with perfusion machines (circuits). Fahy teaches the circuits are advantageous because it provides controlled perfusion of organs, minimizing damage to the organs (col.6-7). At the time of the claimed invention, one of ordinary skill in the art would have been motivated to use the circuit of Fahy in the methods of Luh for its disclosed advantage of controlling and minimizing organ damage during perfusion. Although each of the claimed perfusion temperatures, pressures, amounts of thrombolytic agent and origin of organs are not disclosed, it would have been well within the purview of one of ordinary skill in the art to optimize such parameters as a matter of routine experimentation. Moreover, at the time of the claimed invention, one of ordinary skill in the art would have been motivated by routine practice to optimize the variables of Luh with a reasonable expectation for successfully treating an organ with a perfusion solution.

13. Claims 1, 4 – 10 and 17 – 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dubrul.

Applicant claims a method for treating an organ with a thrombolytic agent to promote thrombolysis, the method comprising perfusing the organ with a perfusion solution comprising a thrombolytic agent. Perfusion is conducted until thrombolysis is substantially complete and parameters are within acceptable limits. The thrombolytic agent is selected from streptokinase,

urokinase, alteplase, tenecteplase, tissues plasminogen activators, anistreptase, anisoylated streptokinase, reteplase, and mutant tissue plasminogen activators, specifically streptokinase in the amount of 10,000 -- 1,500,000 IU, 100,000 -- 300,000 IU, 5000 – 58,000,000 IU or about 10 – 30 more units, or 250,000 IU. The organ is perfused for 1 – 20 hours, at least 4 hours or 4 – 12 hours and is selected from a heart, liver, kidney, lung, pancreas and intestine.

Dubrul teaches methods for dissolving thrombi within intestines, wherein a thrombolytic agent such as urokinase is dispensed (abstract). Other thrombolytic agents are named to include streptokinase and tissue plaminogen activators (col.1 line 48-57).

Dubrul does not teach the method with the claimed agent amounts or time perfused. However, it would have been well within the purview of one of ordinary skill in the art to optimize such parameters as a matter of routine experimentation. Moreover, at the time of the claimed invention, one of ordinary skill in the art would have been motivated by routine practice to optimize the variables of Dubrul with a reasonable expectation for successfully treating an organ with a perfusion solution.

14. Claims 1 – 4, 9 – 10 and 12 – 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yland.

Applicant claims a method for treating an organ with a thrombolytic agent to promote thrombolysis, the method comprising perfusing the organ with a perfusion solution comprising a thrombolytic agent. The organ is removed from a human; or is selected from a heart, liver, kidney, lung, pancreas and intestine. Perfusion comprises connecting the organ to a perfusion circuit and recirculating the solution through the organ and is conducted until thrombolysis is

substantially complete and parameters are within acceptable limits. The thrombolytic agent is administered at 5000 – 58,000,000 IU or about 10 – 30 more units or 250,000 IU. The perfusion circuit has a systolic pressure of less than 60 mm Hg, 45 – 60 mm Hg or about 50 mm Hg and the perfusion solution is recirculated at about 2 · 10C or about 5C for 1 – 20 hours, at least 4 hours or 4 – 12 hours.

Yland teaches machine perfusion is effective for organ and kidney preservation (abstract). Specifically, that machine perfusion can be high or low flow at 6 – 9C. Yland teaches methods wherein kidneys are removed, high and low flow machine flushed (perfused) with heparin (a thrombolytic agent) at 0 – 4C for about 72 hours (p.536, Materials and Methods). Perfusion pressure are 30 – 40 mm Hg with a controlled perfusion curcuit (p.536, Equipment). Yland teaches that such methods better preserves the organ (p.539).
Yland does not teach the method with a harvested human organ, the claimed amounts of agent, time or pressures perfused. However, it would have been well within the purview of one of ordinary skill in the art to optimize such parameters as a matter of routine experimentation. Moreover, at the time of the claimed invention, one of ordinary skill in the art would have been motivated by routine practice to optimize the variables of Yland with a reasonable expectation for successfully treating an organ with a perfusion solution.

15. Claims 1 – 10 and 12 – 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yamaueni, Grundy or Pineo in view of Fahy (US 5472876).

Applicant claims a method for treating an organ with a thrombolytic agent to promote thrombolysis, the method comprising perfusing the organ with a perfusion solution comprising a

thrombolytic agent. The organ is removed from a human; or is selected from a heart, liver, kidney, lung, pancreas and intestine. The thrombolytic agent is selected from streptokinase, urokinase, alteplase, tenecteplase, tissues plasminogen activators, anistreptase, anisoylated streptokinase, reteplase, and mutant tissue plasminogen activators. Specifically streptokinase in the amount of 10,000 – 1,500,000 IU; 100,000 – 300,000 IU; 5000 – 58,000,000 IU or about 10 – 30 more units; or 250,000 IU. Perfusion comprises connecting the organ to a perfusion circuit and recirculating the solution through the organ and is conducted until thrombolysis is substantially complete and parameters are within acceptable limits. The perfusion circuit has a systolic pressure of less than 60 mm Hg, 45 – 60 mm Hg, or about 50 mm Hg and the perfusion solution is recirculated at about 2 – 10C or about 5C for about 1 – 20 hours, at least 4 hours or 4 – 12 hours.

Yamauchi teaches methods wherein livers are flushed (perfused) with solutions containing 7500 IU streptokinase at 4C, wherein microvascular procurement of the liver is improved (abstract, methods) and thrombus formation is prevented (p.1781, Results). Yamauchi additionally teaches that streptokinase is a known potent fibrinolytic drug for treating thrombosis and thrombosis related diseases (p.1783).

Gundry teaches a method wherein a heart is harvested and perfused with 200,000 units of streptokinase at 30 mm Hg, wherein clots are dissolved (or effects thrombolysis) (abstract).

Pineo teaches a method wherein a kidney is infused with streptokinase to effect thrombolysis (abstract). Specifically, 100,000 – 520,000 IU were administered over 16.5 hours (p.1223). Pineo teaches that renal thrombus should be treated with an infusion of a thrombolytic agent such as streptokinase (p.1224)

The above references do not teach the methods wherein the organs are perfused with a perfusion circuit (or machine) at the claimed pressures, temperatures or time periods. However, Fahy teaches methods for perfusing organs wherein the organ is flushed (or perfused) with a perfusion solution comprising thrombolytic agent (heparin) and vasodilators (col.23 line 4-9). The excised organs are perfused at pressures of 20 – 70 mmHg (col.24 line 32-38) at 0 – 15C (col.24 line 58-62) and may be selected from a heart, kidney, or liver (col.5 line 53-55). Fahy teaches the circuits are advantageous because it provides controlled perfusion of organs, minimizing damage to the organs (col.6-7). At the time of the claimed invention, one of ordinary skill in the art would have been motivated to use the circuit of Fahy in the methods of Yamauchi, Gundry or Pineo for its disclosed advantage of controlling and minimizing organ damage during perfusion. Although each of the claimed perfusion temperatures, pressures, amounts of thrombolytic agent and origin of organs are not disclosed, it would have been well within the purview of one of ordinary skill in the art to optimize such parameters as a matter of routine experimentation. Moreover, at the time of the claimed invention, one of ordinary skill in the art would have been motivated by routine practice to optimize the variables of Yamauchi, Gundry or Pineo with a reasonable expectation for successfully treating an organ with a perfusion solution.

16. Claims 1 – 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yamauchi, Grundy, or Pineo in view of Luh and Fahy.

Applicant claims a method for treating an organ with a thrombolytic agent to promote thrombolysis, the method comprising perfusing the organ with a perfusion solution comprising a

thrombolytic agent. The organ is removed from a human; or is selected from a heart, liver, kidney, lung, pancreas and intestine. The thrombolytic agent is selected from streptokinase, urokinase, alteplase, tenecteplase, tissues plasminogen activators, anistreptase, anisoylated streptokinase, reteplase, and mutant tissue plasminogen activators. Specifically streptokinase in the amount of 10,000 – 1,500,000 IU; 100,000 – 300,000 IU; 5000 – 58,000,000 IU or about 10 – 30 more units; or 250,000 IU. Perfusion comprises connecting the organ to a perfusion circuit and recirculating the solution through the organ and is conducted until thrombolysis is substantially complete and parameters are within acceptable limits. The perfusion circuit has a systolic pressure of less than 60 mm Hg, 45 – 60 mm Hg, or about 50 mm Hg and the perfusion solution is recirculated at about 2 – 10C or about 5C for about 1 – 20 hours, at least 4 hours or 4 12 hours.

Yamauchi teaches methods wherein livers are flushed (perfused) with solutions containing 7500 IU streptokinase at 4C, wherein microvascular procurement of the liver is improved (abstract, methods) and thrombus formation is prevented (p.1781, Results). Yamauchi additionally teaches that streptokinase is a known potent fibrinolytic drug for treating thrombosis and thrombosis related diseases (p.1783).

Gundry teaches a method wherein a heart is harvested and perfused with 200,000 units of streptokinase at 30 mm Hg, wherein clots are dissolved (or effects thrombolysis) (abstract).

Pineo teaches a method wherein a kidney is infused with streptokinase to effect thrombolysis (abstract). Specifically, 100,000 – 520,000 IU were administered over 16.5 hours (p.1223). Pineo teaches that renal thrombus should be treated with an infusion of a thrombolytic agent such as streptokinase (p.1224).

The above references do not teach the methods wherein the perfusion solutions further contain a vasodilator. However, Luh teaches methods wherein organs are perfused with a solution containing heparin, urokinase (thrombolytic agents), PGE1, and NO (vasodilators) wherein thrombus formation was inhibited (abstract). Specifically, Luh teaches that urokinase and PGE1 are added to perfusion solutions to improve organ vasodilation and thrombolysis (p.2025). At the time of the claimed invention, one of ordinary skill in the art would have been motivated to include a vasodilator in the perfusion solutions of Yamauchi, Gundry or Pineo with a reasonable expectation for successfully improving thrombolysis, as evidenced by Luh.

The above references do not teach the methods wherein the organs are perfused with a perfusion circuit (or machine) at the claimed pressures, temperatures or time periods. However, Fahy teaches methods for machine perfusing organs wherein the organ is flushed (or perfused) with a perfusion solution comprising thrombolytic agent (heparin) and vasodilators (col.23 line 4-9). The excised organs are perfused at pressures of 20 – 70 mmHg (col.24 line 32-38) at 0 – 15C (col.24 line 58-62) and may be selected from a heart, kidney, or liver (col.5 line 53-55). Fahy teaches the circuits are advantageous because it provides controlled perfusion of organs, minimizing damage to the organs (col.6-7). At the time of the claimed invention, one of ordinary skill in the art would have been motivated to use the circuit of Fahy in the methods of Yamauchi, Gundry or Pineo for its disclosed advantage of controlling and minimizing organ damage during perfusion. Although each of the claimed perfusion temperatures, pressures, amounts of thrombolytic agent and origin of organs are not disclosed, it would have been well within the purview of one of ordinary skill in the art to optimize such parameters as a matter of routine experimentation. Moreover, at the time of the claimed invention, one of ordinary skill in

the art would have been motivated by routine practice to optimize the variables of Yamauchi, Gundry or Pineo with a reasonable expectation for successfully treating an organ with a perfusion solution.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ruth A. Davis whose telephone number is 703-308-6310. The examiner can normally be reached on M-H (7:00-4:30); altn. F (7:00-3:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 703-308-0196. The fax phone number for the organization where this application or proceeding is assigned is 703-308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Ruth A. Davis; rad
November 13, 2003.